Oiginal Article

Glucomannan Ameliorates Hepatic Lipid Metabolism and Glucose Homeostasis in Rat Models Fed a High-Fat Diet

Roaa M. Alreemi[1], Khadija S. Radhi[2], Taqwa Bushnaq[2], Ohud Saleh[1], Reem S. Alazragi[1*]

[1]Department of Biochemistry, College of Science, University of Jeddah, Jeddah 21959, Saudi Arabia. [2]Department of Food Science and Nutrition, College of Science, Taif University, Taif 21944, Saudi Arabia.

Abstract

This work was conducted to investigate the effects of glucomannan extracted from konjac (KGM) on high-fat diet (HFD)-)-induced lipid metabolic abnormalities and dysglycaemia and explore its possible mechanisms. Sixty adult male albino rats (Sprague-Dawley) were separated into five groups: G1 (control) fed a basal fat diet (BFD); G2, fed a high-fat modified diet containing 20% fat (HFD); and G3, G4, and G5, fed an HFD supplemented with three levels of KGM (1, 5, and 10 g/100 g diet, respectively). Results showed that rats fed HFDs developed hepatic glucose and lipid abnormalities. Glucomannan administration normalized hepatic glucose metabolism in HFD-fed rats with low fasting blood glucose. KGM may postpone obesity, diabetes, and associated consequences as a dietary intervention. To sum up, supplementing rats with 10 g/100g dietary Glucomannan improves blood lipid levels, lipid metabolism in the liver, and glucose regulation. This suggests that KGM could be supplied in the future as a potential anti-hyperglycaemic and antilipidemic dietary supplement.

Keywords: Konjac glucomannan, High-fat diet, Lipid metabolism, Glucose homeostasis

Introduction

Alterations in dietary regimens and inactive lifestyles are the main causes of the increased frequency of chronic diseases [1]. On the other hand, extreme fat intake disturbs the balance between energy input and energy output, thus promoting obesity [2]. Commonly, increased dietary fat leads to increased lipid circulation in the bloodstream, causing the accumulation of fat in adipose tissue and the liver, and disturbs lipid metabolism [3, 4]. Different metabolic disorders correlated with an excess of dietary fat such as hypertension, hyperinsulinemia, and diabetes, cause public health challenges [5]. These metabolic disorders cause pathogenic mechanisms that are distinguished by chronically elevated free fatty acids (FFAs) and insulin secretion in the bloodstream [6]. Fatty liver may be explained by the accumulation of FFAs from a high-fat diet (HFD), which could disrupt glucose consumption via the glycolytic pathway and increase insulin resistance in peripheral cells, leading to hyperinsulinemia Transcriptional regulation of lipid metabolism by fatty acids: a key determinant of pancreatic β-cell function [7].

Chronic hyperglycemia may be treated by dietary mediation due to its potential to reduce inflammation, boost insulin sensitivity, promote the growth of good intestinal flora, and maintain equilibrium in glucolipid metabolism [8, 9]. Plant extracts, fermentation products, and functional oligosaccharides are among the many functional foods that are believed to be helpful in the treatment of metabolic diseases [10]. Functional oligosaccharides are hydrolytic products of polysaccharides that cannot be digested in the gastrointestinal tract (GI) but are used as probiotics [11]. They are generally accepted as safe substances with several beneficial health effects, the most important of which is the ability to control glucose levels in the body [12, 13].

Polysaccharide glucomannan is water soluble, is derived from the tuber of the *Amorphophallus konjac* plant, and consists mostly of D-glucose and D-mannose connected by -1,4-glycosidic linkages [14]. Alkaloids, pectin, amino acids, and trace elements including potassium, phosphorus, and selenium may be found in konjac glucomannan (KGM) [15]. Moreover, KGM can be used in pharmaceutical and cosmetic industries due to its good quality thickening, solidity, and biocompatibility properties [16]. It can modulate immunity [17], regulate gut microbiota, exert an anti-obesity effect [18,

Address for correspondence: Reem S. Alazragi, Department of Biochemistry, College of Science, University of Jeddah, Jeddah 21959, Saudi Arabia.
rsalazragi@uj.edu.sa

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19], enhance the role of isolated islets in the primary cells of diabetic mice [20], and improve the hypoglycaemic impact of metformin [21].

Materials and Methods

Materials

Glucomannan pure powder from Konjac Root was purchased as a dietary supplement from Now Foods Co., Bloomingdale, IL., USA.

Animals

The study used adult male albino rats (Sprague-Dawley) weighing 98.7±5g. Rats were kept in stainless steel cages within an air-conditioned animal house at 24 °C, fed a basal diet (AIN-93), and permitted water ad libitum through the experimental period (6 weeks).

Experimental Design

Sixty male rats were separated into five groups (12 rats/group) as follows:

1. Control group: Fed a basal diet (AIN-93) (BFD).
2. High-fat diet group (HFD): Fed a modified AIN-93 diet for 42 days containing 20 g fat/100 g diet.
3. High-fat diet low glucomannan group (HFD+LKGM): Fed an HFD supplemented with 1 g KGM/100 g diet.
4. High-fat diet medium glucomannan group (HFD+MKGM): Fed an HFD supplemented with 5 g KGM/100 g diet.
5. High-fat diet high glucomannan group (HFD+HKGM): Fed an HFD supplemented with 10 g KGM/100 g diet.

Sample Collection and Biochemical Assessment

After 42 days, blood was drawn from the hepatic portal vein of rats anesthetized with ether, and fasted overnight. The blood tubes were centrifuged at 4000 x g and 25 °C for 15 minutes to separate the serum. Serum samples were collected in sterile plastic tubes and frozen at -20 ºC for subsequent biochemical studies. Livers were separated, rinsed, and washed with saline (NaCl 0.9%) and then blotted on filter paper. Livers were quickly frozen and stored at -20 ºC for glycogen analysis. Liver glycogen and serum levels of total cholesterol (TC), triacylglycerols (TG), LDL-c, HDL-c, FFA, glucose, insulin, and activities of alanine transaminase (ALT), aspartate transaminase (AST), fatty acid synthase (FAS), acetyl-CoA carboxylase (ACC), pyruvate carboxylase (PC), and phosphoenolpyruvate carboxy-kinase (PEP-CK) were determined by analytical methods.

Statistical Analysis

SPSS version 20.0 was used to carry out statistical analyses, and the results are reported as means of standard error (SE). T-tests were used to determine statistically significant differences between the groups. Results were considered significant at ($p<0.01$).

Results and Discussion

Results in **Table 1** revealed that serum concentrations of TG, TC, and LDL-cholesterol were elevated significantly ($p<0.01$) in rats fed an HFD compared with the BFD group and gradually normalized by KGM supplementation. The level of serum HDL-cholesterol was significantly lower ($p<0.01$) in the HFD group than in the BFD group and was gradually increased by adding KGM (G3-G5).

Table 1. Effect of various treatments on serum levels of TG, TC, HDL-c, and LDL-c

Groups	TG (mg/dl)	TC (mg/dl)	HDL-cholesterol (mg/dl)	LDL-cholesterol (mg/dl)
BFD	102.5^{a}±2.3	166.5^{a}±0.15	55.8^{a}±0.05	85.7^{a}±0.03
HFD	125.3^{b}±3.7	215.3^{b}±0.11	35.7^{b}±0.03^{ac}	142.2^{b}±0.20
HFD+LKGM	122.7^{b}±3.3	198.3^{c}±0.53	45.1^{c}±0.09	133.5^{c}±0.15
HFD+MKGM	104.5^{a}±2.1	173.1^{d}±0.23	50.2^{d}±0.03	93.2^{d}±0.06
HFD+HKGM	103.8^{a}±2.5	172.5^{d}±0.12	51.9^{d}±0.08	95.3^{d}±0.05

BFD=Basal fat diet; HFD=High-fat diet; LKGM=Low glucomannan; MKGM=Medium glucomannan; HKGM=High glucomannan (n=12)

KGM supplementation has a significant effect ($p<0.01$) on serum levels of FFA and FAS activity as well as on acetyl CoA carboxylase (ACC) activity **(Table 2)**. Increased levels of enzymes were detected in the HFD group, as compared to the BFD group, following ingestion.

Table 2. Effect of various treatments on serum levels of FFA, FAS, and ACC activities

Groups	FFA (µmol/ml)	FAS (ng/ml)	ACC (ng/ml)
BFD	0.479 ^{a} ±0.05	32.25 ^{a} ±6.10	6.15 ^{a} ±1.05
HFD	1.292 ^{b} ±0.06	52.7 ^{b} ±8.10	12.82 ^{b} ±1.00
HFD+LKGM	1.154 ^{b} ±0.04	49.11 ^{b} ±4.25	10.21 ^{c} ±0.9

HFD+MKGM	0.905 [c] ±0.08	38.33 [c] ±5.20	6.95 [d] ±0.75
HFD+HKGM	0.913 [c] ±0.03	39.05 [c] ±4.15	6.80 [d] ±1.00

BFD=Basal fat diet; HFD=High-fat diet; LKGM=Low glucomannan; MKGM=Medium glucomannan; HKGM=High glucomannan (n=12).

HFD increased glucose and insulin levels over those of the control group. Meanwhile, KGM supplementation significantly downregulated fasting glucose levels depending on the given doses (by 8.1%, 46.8%, and 49.7%, respectively) over those of the HDF group. Furthermore, KGM supplementation significantly decreased insulin levels (by 4.7%, 46.0%, and 48.2%, respectively) over those of the HFD group. An HFD significantly reduced liver glycogen over that of the control group. In contrast to the HFD group, KGM supplementation increased liver glycogen levels in a dose-dependent manner **(Table 3)**.

Table 3. Effect of various treatments on serum levels of glucose, insulin, and liver glycogen

Groups	Glucose (mg/dl)	Insulin (ng/ml)	Glycogen (g/dl)
BFD	95.3 [a] ±3.2	5.80[a]±0.8	4.55[a]±0.35
HFD	198.5[b]±1.5	11.02[b]±0.1	0.15[b]±0.02
HFD+LKGM	182.3[c]±2.2	10.50[b]±0.7	1.80[c]±0.25
HFD+MKGM	105.5[d]±1.5	5.95[a]±0.5	3.00[d]±0.30
HFD+HKGM	99.8[a]±3.2	5.70[a]±0.9	4.15[a]±0.45

BFD=Basal fat diet; HFD=High-fat diet; LKGM=Low glucomannan; MKGM=Medium glucomannan; HKGM=High glucomannan (n=12)

Table 4 showed an increase in the level of liver enzyme activities in the HFD group compared with that seen in the BFD group, and under KGM supplementation these values decreased gradually (by 4–6%, 15.8%, and 22.6% for ALT, respectively and by 3.4%, 32.5%, and 43.5% for AST, respectively) compared with the HDF group.

Table 4. Effect of various treatments on serum enzyme activities ALT and AST in all rat groups

Groups	ALT (U/L)	AST (U/L)
Negative Control (C)	52.7 [a] ±5.8	49.3 [a] ±5.2
Positive Control (HFD)	70.5 [b] ±6.5	92.3 [b] ±7.9
HFD+LKGM	67.2 [b] ±6.1	89.1 [b] ±6.3
HFD+MKGM	59.3 [c] ±4.9	62.3 [c] ±3.7
HFD+HKGM	54.5 [d] ±4.8	52.1 [d] ±3.9

BFD=Basal fat diet; HFD=High-fat diet; LKGM=Low glucomannan; MKGM=Medium glucomannan; HKGM=High glucomannan (n=12)

Table 5 revealed the reduction of PC and phosphoenolpyruvate carboxykinase (PEP-CK) activities in rats fed an HFD compared to control rats. Supplementing glucomannan at a high dose (10 g%) modulated the activities of both enzymes as compared to low (1 g%) and moderate (5 g%) doses of glucomannan.

Table 5. Effect of various treatments on liver PC and PEP-CK activities

Groups	PC (pmol/min/mg protein)	PEPCK (nmol PEP/min/mg protein)
BFD	163.3 [a] ±7.2	68.4 [a] ±1.7
HFD	115.2 [b] ±4.3	49.3 [b] ±2.4
HFD+LKGM	125.3 [c] ±5.0	50.1 [b] ±1.2
HFD+MKGM	148.5 [d] ±3.5	55.0 [c] ±1.5
HFD+HKGM	160.3 [a] ±5.8	61.4 [d] ±1.8

BFD=Basal fat diet; HFD=High-fat diet; LKGM=Low glucomannan; MKGM=Medium glucomannan; HKGM=High glucomannan (n=12).

Researchers in the fields of nutrition and medicine have shown increasing interest in a variety of polysaccharides extracted from higher plants, algae, mushrooms, and yeast in recent years. The reasons for this interest include the low toxicity, rarity, and mildness of the side effects of these substances as well as their comparatively low cost and the wide range of therapeutic functions they can perform. β-glucan and mannan are the two types of polysaccharides that have been most researched [22]. It has been demonstrated that polysaccharides activate macrophages in vivo by interacting with the mannose receptor [23, 24]. As a result, activating macrophages enables those cells to clear the blood of atherogenic lipoproteins more efficiently.

TG and TC are normally released from the liver [25], whereas FFA in serum might be transferred to the liver for de novo lipogenesis [26]. Serum levels of HDL-C and LDL-C are also closely related to lipid metabolism. In the present study, serum concentrations of TG, TC, FFA, and LDL-c were significantly higher in rats fed HFD than in rats fed BFD, indicating increased endogenous lipid transport. This result is consistent with studies that have found high plasma concentrations of TC and TG attributable to lipid overload in the liver due to high dietary fat intake [27, 28].

Supplementing diets with glucomannan resulted in substantial reductions in blood concentrations of TC, TG, and LDL-c, which demonstrates unequivocally that glucomannan influences the regulation of lipid metabolism. This finding was in line with the findings of research conducted on rats that revealed that supplementing the diet with KGM dramatically lowered concentrations of TC, TG, and FFA [29]. In addition, the consumption of dietary glucomannan led to an increase in the serum concentration of HDL-c in rats that had been fed a high-carbohydrate HFD.

It has been shown that glucomannan can reduce hepatic lipid deposition through the activation of adenosine monophosphate-activated kinase (AMPK) and peroxisome proliferator-activated receptors (PPAR) pathways and down-regulation of key lipid metabolism-related genes in mice fed an HFD [30]. This result suggests that the effect of glucomannan on hepatic lipid metabolism in rats may be due to a combination of metabolic mechanisms, including 1) decreased lipid synthesis by activating AMPK phosphorylation and down-regulating the expression of downstream targets of lipid metabolism of AMPK in the liver; and 2) decreased lipid accumulation in rats by simultaneously increasing lipid transport and lipid degradation. Activation of the phosphatidylinositol 3-kinase (PI3K) pathway and regulation of the expression of key genes related to lipid metabolism suggest a function of KGM in the prevention of HFD-induced nonalcoholic fatty liver syndrome (NAFLS) in animals [29]. The effects of glucomannan on fatty acid synthesis and ACC activity in the liver have been investigated.

Increased fatty acid synthesis in the liver was seen in the current study with FAS and ACC activity being considerably upregulated in rats given an HFD compared to those fed a BFD [25]. On the other hand, glucomannan in the diet lowered the activity of these enzymes, indicating that this substance slowed the pace at which lipids were synthesized. It is well known that fatty acid oxidation and hepatic de novo lipogenesis are the major metabolic processes controlling hepatic lipid metabolism [31]. SREBP-1c and PPAR were important regulators of lipogenesis and fatty acid oxidation pathways, respectively, throughout metabolism [32]. By increasing the expression of rate-limiting enzymes such as FAS and ACC, the transcription factor SREBP-1c increases fatty acid and triglyceride production [33]. First, under the regulation of SREBP-1c and FAS, ACC, which acts as the rate-limiting enzyme in the fatty acid production pathway, catalyzes the conversion of acetyl-CoA to malonyl-CoA. As a transcription factor in adipogenesis, peroxisome proliferator-activated receptor (PPAR) contributes to the formation of adipose tissue [14].

Elevated insulin levels stimulate lipogenesis and gluconeogenesis in the liver [34] and muscle tissue [35], two key steps in the synthesis of new lipids. The increased synthesis of saturated and monounsaturated fatty acids and triglycerides is caused by insulin-induced activation of genes involved in lipid metabolism. Glucose fluxes from gluconeogenesis, glycogen synthesis in the liver and muscle, hepatic glycogenolysis, glycolysis, and other pathways contribute to hepatic net glucose production [36], and the liver plays a significant role in glycaemic control between meals through regulating glucose transformation [37]. One of how glucose and glycogen are produced in mammals is the process of gluconeogenesis [38], which involves the conversion of various nutrients (lactic acid, amino acids, glycerol, etc.) into glucose and glycogen. Diabetes and gluconeogenesis are inextricably linked. When gluconeogenesis is more pronounced, the fasting blood sugar level rises. Insulin's roles include the suppression of gluconeogenesis [39], which is the production of glucose, the stimulation of the conversion of glucose into fat, the transport of glucose to adipose tissue, and the storage of glucose. Reducing glycogen formation in the liver, blocking gluconeogenesis in the liver, and keeping fasting blood glucose stable have all been demonstrated as benefits of KGM administration [40]. Therefore, regulation of glycogen synthesis by konjac and inhibition of gluconeogenesis may also be associated with lowering blood glucose levels in rats. The current investigation confirmed previous findings that an HFD depletes liver glycogen reserves. Overfeeding with a great deal of fat causes the liver to produce more glucose, which leads to higher fasting levels of blood sugar. Compared to the HFD group, the liver glycogen level rose in proportion to the amount of glucomannan supplementation. Indirect glycaemic control using the growth of gut probiotics has been attributed to glucomannan [21]. Glucomannan can also control blood sugar levels by modulating glucose metabolism in the liver.

KGM has been shown to lower blood sugar levels through several mechanisms, including blocking the intestinal absorption of cholesterol and bile acids [41]. KGM's hypoglycaemic mechanism mostly resides in its flow properties as a soluble dietary fiber with high viscosity and significant satiety. KGM may quickly expand in the stomach after absorbing water, forming a very viscous konjac gum solution that the stomach struggles to digest. This property slows gastric emptying, lengthens the time it takes for food to reach the small intestine from the stomach, and creates a layer of stationary water on the surface of the intestinal mucosa [15]. Blood sugar levels are lowered because this slows the intestinal absorption of glucose and prevents the digestion and absorption of most carbs and monosaccharides. Recent studies have indicated that a diet high in glucomannan soluble fiber can help control blood sugar levels and reduce the risk of diabetes [42].

Both ALT and AST activities are often regarded as reliable markers of liver injury because they are released into the bloodstream from damaged hepatic cell membranes [43, 44]. In the present study, serum levels of ALT and AST were measured after consumption of glucomannan for eight weeks indicating the role of glucomannan in preventing liver damage. The impairment of the liver is linked to metabolic abnormalities and the development of glucose metabolic diseases [36]. KGM influenced glycogen accumulation by modulating the enzymatic activity of PC, the rate-limiting enzyme in gluconeogenesis and glycolysis. Indirect glycaemic modulation by KGM has been seen, with reports showing that it promotes the growth of gut probiotics [21]. As a result, we hypothesized that KGM may directly control blood glucose by influencing hepatic glucose metabolism.

Elevated KGM supplementation to 10% of the diet enhanced the activities of gluconeogenic regulatory enzymes including PC and PEPCK. Liver, adipose tissue, and pancreatic cells have all been researched for their roles and control of PC in metabolism due to PC's contribution to fatty acid synthesis, glucose homeostasis, and insulin secretion, respectively [45]. Consistent with its essential function in controlling TCA cycle activity, gluconeogenesis, and overall energy balance, PC activity is tightly regulated [46].

Conclusion

Rats fed an HFD developed hepatic glucose and lipid abnormalities. Glucomannan administration normalized the hepatic glucose metabolism in HFD-fed rats with low fasting blood glucose. Dietary KGM may be effective in preventing obesity and diabetes as a nutritional intervention. Supplementing HFD-fed rats with 10 g/100 g diet glucomannan improves blood lipids, hepatic lipid metabolism, and glucose hemostasis.

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References

1. Kim S, Hong J, Jeon R, Kim HS. Adzuki bean ameliorates hepatic lipogenesis and proinflammatory mediator expression in mice fed a high-cholesterol and high-fat diet to induce nonalcoholic fatty liver disease. Nutr Res. 2016;36(1):90-100.
2. Venkatakrishnan K, Chiu HF, Wang CK. Extensive review of popular functional foods and nutraceuticals against obesity and its related complications with a special focus on randomized clinical trials. Food Funct. 2019;10(5):2313-29.
3. Charbonneau A, Melancon A, Lavoie C, Lavoie JM. Alterations in hepatic glucagon receptor density and in Gsα and Giα2 protein content with diet-induced hepatic steatosis: Effects of acute exercise. Am J Physiol Endocrinol Metab. 2005;289(1):E8-14.
4. Chen Y, Jin L, Li Y, Xia G, Chen C, Zhang Y. Bamboo-shaving polysaccharide protects against high-diet induced obesity and modulates the gut microbiota of mice. J Funct Food. 2018;49:20-31.
5. Coelho DF, Pereira-Lancha LO, Chaves DS, Diwan D, Ferraz R, Campos-Ferraz PL, et al. Effect of high-fat diets on body composition, lipid metabolism and insulin sensitivity, an d the role of exercise on these parameters. Braz J Med Biol Res. 2011;44(10):966-72.
6. Denisenko YK, Kytikova OY, Novgorodtseva TP, Antonyuk MV, Gvozdenko TA, Kantur TA. Lipid-induced mechanisms of metabolic syndrome. J Obes. 2020;2020:5762395.
7. Fatehi-Hassanabad Z, Chan CB. Transcriptional regulation of lipid metabolism by fatty acids: A key determinant of pancreatic β-cell function. Nutr Metab (Lond). 2005;2(1):1-12.
8. Kim Y, Keogh J, Clifton P. Probiotics, prebiotics, synbiotics and insulin sensitivity. Nutr Res Rev. 2018;31(1):35-51.
9. Müller M, Canfora EE, Blaak EE. Gastrointestinal transit time, glucose homeostasis and metabolic health: Modulation by dietary fibers. Nutrients. 2018;10(3):275.
10. Adefegha SA. Functional foods and nutraceuticals as dietary intervention in chronic diseases; novel perspectives for health promotion and disease prevention. J Diet Suppl. 2018;15(6):977-1009.
11. Ouyang D, Deng J, Zhou K, Liang Y, Chen Y, Wang D, et al. The effect of deacetylation degree of konjac glucomannan on microbial metabolites and gut microbiota in vitro fermentation. J Funct Food. 2020;66:103796.
12. Swennen K, Courtin CM, Delcour JA. Non-digestible oligosaccharides with prebiotic properties. Crit Rev Food Sci Nutr. 2006;46(6):459-71.
13. Ibrahim OO. Functional oligo-saccharides: Chemicals structure, manufacturing, health benefits, applications and regulations. J Food Chem Nanotechnol. 2018;4(4):65-76.
14. Zang Y, Zhang L, Igarashi K, Yu C. The anti-obesity and anti-diabetic effects of kaempferol glycosides from unripe soybean leaves in high-fat-diet mice. Food Funct. 2015;6(3):834-41.
15. Devaraj RD, Reddy CK, Xu B. Health-promoting effects of konjac glucomannan and its practical applications: A critical review. Int J Biol Macromol. 2019;126:273-81.
16. Yang D, Yuan Y, Wang L, Wang X, Mu R, Pang J, et al. A review on konjac glucomannan gels: Microstructure and application. Int J Mol Sci. 2017;18(11):2250.
17. Kiyohara H, Matsuzaki T, Yamada H. Intestinal Peyer's patch-immunomodulating glucomannans from rhizomes of Anemarrhena asphodeloides Bunge. Phytochemistry. 2013;96:337-46.
18. Wang H, Zhang X, Wang S, Li H, Lu Z, Shi J, et al. Mannan-oligosaccharide modulates the obesity and gut microbiota in high-fat diet-fed mice. Food Funct. 2018;9(7):3916-29.

19. Liu X, Chen S, Yan Q, Li Y, Jiang Z. Effect of Konjac mannan oligosaccharides on diphenoxylate-induced constipation in mice. J Funct Food. 2019;57:399-407.
20. Lu XJ, Chen XM, Fu D-X, Cong W, Ouyang F. Effect of Amorphophallus Konjac oligosaccharides on STZ-induced diabetes model of isolated islets. Life Sci. 2002;72(6):711-9.
21. Zheng J, Li H, Zhang X, Jiang M, Luo C, Lu Z, et al. Prebiotic mannan-oligosaccharides augment the hypoglycemic effects of metformin in correlation with modulating gut microbiota. J Agric Food Chem. 2018;66(23):5821-31.
22. Korolenko TA, Bgatova NP, Vetvicka V. Glucan and mannan—two peas in a pod. Int J Mol Sci. 2019;20(13):3189.
23. Korolenko T, Kisarova YA, Filjushina E, Dergunova M, Machova E. Macrophage stimulation and β-dglucans as biological response modifiers: The role in experimental tumor development. Handbook of Macrophages: Life Cycle, Functions and Diseases 2012. p. 249-75.
24. Korolenko TA, Johnston TP, Machova E, Bgatova NP, Lykov AP, Goncharova NV, et al. Hypolipidemic effect of mannans from C. albicans serotypes a and B in acute hyperlipidemia in mice. Int J Biol Macromol. 2018;107(Pt B):2385-94.
25. Zhao H, Wu Z, Zhou Y, Guo D, Wang H, Chen X. Hepatic lipid metabolism and oxidative stress responses of grass carp (Ctenopharyngodon idella) fed diets of two different lipid levels against Aeromonas hydrophila infection. Aquaculture. 2019;509:149-58.
26. Kawano Y, Cohen DE. Mechanisms of hepatic triglyceride accumulation in non-alcoholic fatty liver disease. J Gastroenterol. 2013;48:434-41.
27. Straczkowski M, Kowalska I, Dzienis-Straczkowska S, Kinalski M, Gorski J, Kinalska I. The effect of exercise training on glucose tolerance and skeletal muscle triacylglycerol content in rats fed with a high-fat diet. Diabetes Metab. 2001;27(1):19-23.
28. Drouin R, Robert G, Milot M, Massicotte D, Péronnet F, Lavoie C. Swim training increases glucose output from liver perfused in situ with glucagon in fed and fasted rats. Metabolism. 2004;53(8):1027-31.
29. Shang W, Li H, Strappe P, Zhou Z, Blanchard C. Konjac glucomannans attenuate diet-induced fat accumulation on livers and its regulation pathway. J Funct Food. 2019;52:258-65.
30. Zhai X, Lin D, Zhao Y, Li W, Yang X. Enhanced anti-obesity effects of bacterial cellulose combined with konjac glucomannan in high-fat diet-fed C57BL/6J mice. Food Funct. 2018;9(10):5260-72.
31. Nguyen P, Leray V, Diez M, Serisier S, Bloc'h JL, Siliart B, et al. Liver lipid metabolism. J Anim Physiol Anim Nutr (Berl). 2008;92(3):272-83.
32. Lee HS, Lee SJ, Yu HJ, Lee JH, Cho HY. Fermentation with Lactobacillus enhances the preventive effect of garlic extract on high fat diet-induced hepatic steatosis in mice. J Funct Food. 2017;30:125-33.
33. Yang Y, Li W, Liu Y, Sun Y, Li Y, Yao Q, et al. Alpha-lipoic acid improves high-fat diet-induced hepatic steatosis by modulating the transcription factors SREBP-1, FoxO1 and Nrf2 via the SIRT1/LKB1/AMPK pathway. J Nutr Biochem. 2014;25(11):1207-17.
34. Yang JY, Lee SJ, Park HW, Cha YS. Effect of genistein with carnitine administration on lipid parameters and obesity in C57Bl/6J mice fed a high-fat diet. J Med Food. 2006;9(4):459-67.
35. Dobrzyn P, Pyrkowska A, Jazurek M, Szymanski K, Langfort J, Dobrzyn A. Endurance training-induced accumulation of muscle triglycerides is coupled to upregulation of stearoyl-CoA desaturase 1. J Appl Physiol. 2010;109(6):1653-61.
36. Petersen MC, Vatner DF, Shulman GI. Regulation of hepatic glucose metabolism in health and disease. Nat Rev Endocrinol. 2017;13(10):572-87.
37. Mokadem M, Zechner JF, Margolskee RF, Drucker DJ, Aguirre V. Effects of Roux-en-Y gastric bypass on energy and glucose homeostasis are preserved in two mouse models of functional glucagon-like peptide-1 deficiency. Mol Metab. 2014;3(2):191-201.
38. Guasch-Ferré M, Santos JL, Martínez-González MA, Clish CB, Razquin C, Wang D, et al. Glycolysis/gluconeogenesis-and tricarboxylic acid cycle–related metabolites, Mediterranean diet, and type 2 diabetes. Am J Clin Nutr. 2020;111(4):835-44.
39. Hatting M, Tavares CD, Sharabi K, Rines AK, Puigserver P. Insulin regulation of gluconeogenesis. Ann N Y Acad Sci. 2018;1411(1):21-35.
40. Tang L, Luo K, Liu C, Wang X, Zhang D, Chi A, et al. Decrease in myostatin by ladder-climbing training is associated with insulin resistance in diet-induced obese rats. Chin Med J. 2014;127(12):2342-9.
41. Chen HL, Sheu WHH, Tai TS, Liaw YP, Chen YC. Konjac supplement alleviated hypercholesterolemia and hyperglycemia in type 2 diabetic subjects—A randomized double-blind trial. J Am Coll Nutr. 2003;22(1):36-42.
42. McCarty MF. Nutraceutical resources for diabetes prevention–An update. Med Hypotheses. 2005;64(1):151-8.
43. Ashouri S, Keyvanshokooh S, Salati AP, Johari SA, Pasha-Zanoosi H. Effects of different levels of dietary selenium nanoparticles on growth performance, muscle composition, blood biochemical profiles and antioxidant status of common carp (Cyprinus carpio). Aquaculture. 2015;446:25-9.
44. Meng XL, Li S, Qin CB, Zhu ZX, Hu WP, Yang LP, et al. Intestinal microbiota and lipid metabolism responses in the common carp (Cyprinus carpio L.) following copper exposure. Ecotoxicol Environ Saf. 2018;160:257-64.
45. Jitrapakdee S, Vidal-Puig A, Wallace JC. Anaplerotic roles of pyruvate carboxylase in mammalian tissues. Cell Mol Life Sci. 2006;63(7-8):843-54.
46. Wang D, Yang H, De Braganca KC, Lu J, Shih LY, Briones P, et al. The molecular basis of pyruvate carboxylase deficiency: Mosaicism correlates with prolonged survival. Mol Genet Metab. 2008;95(1-2):31-8.